



Problems at the pump? Findings of a recent federal report on oxygenated fuels do little to dispel debate over the health effects of MTBE.

substance of the *Report on Carcinogens*, the process by which the report is prepared and reviewed is also being broadened to promote more public input.

Fueling the Debate

Touted as a way to protect public health by decreasing carbon monoxide (CO) emissions from automobiles, oxygenated fuels containing methyl tertiary butyl ether (MTBE) have been blamed anecdotally for causing headaches, dizziness, eye irritation, burning of the nose and throat, disorientation, and nausea in motorists. In addition, studies have shown that MTBE can cause cancer in rats and mice, though it appears to be a less potent carcinogen than many of the other chemicals found in gasoline and exhaust. Most recently, wells that supply drinking water to Santa Monica, California, were shut down due to high levels of MTBE contamination.

Concerns about the health risks of MTBE, combined with doubts about its ability to significantly lower CO emissions, have caused many to question the usefulness of the chemical as a fuel additive. However, proponents point to decreases in nationwide CO levels as evidence that the 1990 amendments to the Clean Air Act, which sparked the widespread use of MTBE by requiring the use of oxygenated fuels in areas with high CO levels, have led to greatly improved air quality.

Disagreement over the safety and practicality of using MTBE in fuels spurred the EPA to request that the White House National Science and Technology Council review studies done on oxygenated fuels and compile the *Interagency Assessment of Oxygenated Fuels*, which was published in

June 1997. The report considers the effects that using MTBE-treated fuel may have on air quality, water quality, fuel economy, engine performance, and human health.

However, the report does not make any policy recommendations about the future of MTBE as a fuel additive. Ronald Melnick, a toxicologist with the NIEHS who contributed to the interagency report, says, "As far as the total picture of exposure and health effects of oxygenated fuels versus nonoxygenated fuels, there is just not enough evidence right now to draw any definitive conclusion on comparative cancer risk."

As for the effectiveness of MTBE, the authors of the report did find evidence that the chemical, under certain conditions, can decrease CO levels, but they also point out that its performance has not met expectations. "The effectiveness of MTBE was based on models that predicted a 25% decline in CO emissions, which we just have not seen," says Melnick. "CO emissions are decreasing, but it's incorrect to say that this is only a result of using oxygenated fuels. A large part of the decrease is due to improved emission control technology." The report notes that MTBE also cuts other harmful emissions such as benzene and possibly 1,3-butadiene, which is 100 times more carcinogenic than the additive, but that it increases emissions of aldehydes such as the metabolite formaldehyde, which the EPA and the IARC have labeled a genotoxin and probable human carcinogen.

How such changes in emissions and in the composition of fuel vapors will affect motorists is still uncertain, the report concludes. "Complaints have been raised and have not been dismissed about acute health effects like dizziness, headaches, [and] nausea," says Melnick. "There seems to be some consistency

in these reports." But the authors of the interagency report could not find enough evidence to support the contention that MTBE, as used in the winter oxygenated fuels program, is significantly increasing these effects at levels over background levels.

According to the report, the interagency assessment "found that chronic noncancer health effects (neurological, developmental, or reproductive) would not likely occur at environmental or occupational exposures to MTBE." However, inhalation of MTBE has been shown to cause cancer in multiple organ sites in rats and mice. "The EPA is working on a health advisory on MTBE that will be issued in the near future," says Robert Hitzig, the technical lead for the EPA's Office of Underground Storage Tanks. "But it's uncertain now whether [MTBE] will be classified as a possible human carcinogen, a probable human carcinogen, or what its classification will be." However, the interagency report points out that the cancer risk to humans posed by MTBE is similar or slightly less than that posed by untreated gasoline vapors.

Though the health effects of MTBE ingestion are less understood than the effects of inhalation, the appearance of the additive in drinking water across the nation has caused concern over this route of exposure. "MTBE absorbs weakly in soil and not very biodegradable," explains Melnick, "so when there are leakages from underground gasoline storage tanks, it travels further in the ground water and persists for long periods of time." Also, MTBE that enters the atmosphere through exhaust and evaporation can fall to earth and flow into surface water reservoirs with precipitation. Recent studies found MTBE in 7% of urban storm water samples and in 5% of well water samples from across the United States. "The health hazards of MTBE in water are debatable," says Hitzig, "but it's not debatable that there are aesthetic problems with it. MTBE has a very low taste and smell threshold, so that if it's in people's water, they probably know it."

It is also unknown if the presence of MTBE in water is taking a toll on aquatic life. Studies so far have focused only on water used for human consumption, but the persistence of the chemical in the environment makes it of particular concern. Also, notes Hitzig, "There's no way of telling how much MTBE has leaked into groundwater. There have been over 300,000 confirmed releases of petroleum from underground storage tanks since 1988, but we don't know what percentage of them had MTBE in them."

MTBE, which is derived from methanol, is now the most widely used oxygenate in the United States. From 1984 to 1995, production has increased by about 26% annually, with 8 billion kg produced in 1995.

Cancer Bytes

Essentially all of the MTBE produced or imported in the United States is used in the oxygenation of gasoline. Gasoline can contain up to 15% MTBE by volume.

In light of the concerns raised over the use of MTBE, many wonder why the oxygenated fuel program was implemented without further research being conducted first. "Congress required the use of oxygenates in the Clean Air Act," says Hitzig. "The EPA is simply following the statute that was passed. There was a lot known about the risks of MTBE at the time, but maybe the people working on the legislation didn't know [that]."

"A program should be evaluated for [MTBE's] effectiveness as well as its health effects before it is put into use," says Melnick. "There are obviously serious questions about MTBE's effectiveness and its role as an environmental contaminant. So the question is, are we gaining sufficient benefits to make this program worthwhile." Much more research will be needed before this question may be answered with any certainty.

Telomerase Gene Identified

One more step toward understanding the uncontrolled proliferation of immortal cancer cells was taken in August as two separate groups identified the putative human telomerase gene for the first time. These results were published almost simultaneously in the scientific journals *Science* and *Cell*.

The gene produces the enzyme necessary to maintain telomeres, the structures at the end of each chromosome. When cells divide they lose, through the normal process of proliferation, a few of the special base pairs that make up the telomeres. For most cells, this is presumably part of the natural aging process of the cell. When these base pairs run out, the cell can no longer divide properly.

However, for several specialized normal cells in the body it is imperative to be able to continue to divide past the limits normally enforced by the length of the telomeres. Two examples include gamete cells, which carry genetic material from one generation to the next, and the cells in a developing embryo. In the delicate mechanics of the cell, the enzyme telomerase is turned on and off as it is needed to maintain the length of the telomeres.

In contrast to specialized cells, normal cells do not express telomerase. In almost all tumor cells, however, telomerase is expressed. When telomerase is turned on inappropriately, the cell can then become immortal, meaning it can continue to divide indefinitely. The discovery of the gene-encoding part of the telomerase enzyme will allow scientists to probe deeper into the

All cancers, scientists have learned in the last 20 years, begin with a malfunction in the genetic machinery of a cell, causing it to duplicate itself without restraint. Such knowledge brings with it not only new hope for stopping these deadly diseases, but also a great challenge for scientists—to discern the location and function of the culprit genes among the over 100,000 in each human cell.

Now, a powerful new tool on the World Wide Web is making this task much more feasible. The Cancer Genome Anatomy Project (CGAP), which was launched in August 1997, provides scientists with data on the genes expressed in cancerous, precancerous, and normal cells from several different tissues and organs. The site, located at <http://www.ncbi.nlm.nih.gov/ncicgap/>, was developed by the National Cancer Institute and the National Library of Medicine. Information accumulated there will allow scientists to determine how gene expression changes as cells become cancerous, and use this knowledge to direct their research toward suspect genes or their protein products.

Such research could lead to new ways to stop malignant tumors, but even if fulfillment of that goal remains elusive, the genetic "fingerprints" in the CGAP gene index will serve other valuable functions. Using this information, doctors will be able to determine if cells are cancerous before a tumor forms by looking at what genes are being expressed in them. This will allow treatment regimens to be started earlier, quite possibly saving the lives of many patients. Doctors could also use this information to better match treatments to patients by using genetics to distinguish cancers that look nearly identical but respond differently to treatments.

Another goal of the CGAP is to promote the development of new technologies that will add to the breadth of information available on the site. Current technology, for example, makes it difficult to sequence the full lengths of the genes expressed in a cell, so much of the CGAP database is made up of expressed sequence tags—short sequences from randomly isolated portions of genes that can be used to identify genes but that do not necessarily contain all of their genetic information. To address this shortcoming, the CGAP has made \$2.5 million in grants available to researchers to develop methods to efficiently map the full-length sequences of all the genes expressed in cells. Other CGAP grants support the development of technologies to scan the genomes of cancer cells and to evaluate molecular changes in tumor specimens.

From the CGAP home page, information on CGAP grants can be found by following the Information link on the left menu bar. Also on this menu bar is a link to a description of one of the newest technologies being used to gather data for the CGAP web site: clicking on the picture of the laser capture microdissection microscope brings users to an account of how this tool allows scientists to isolate only a few cells of interest from a tissue sample for genetic analysis, rather than using larger specimens that may contain several types of cells.

Except for the View Libraries link, all other links on the home page take users to other sites or to information on the methods used to create the CGAP database. By following the View Libraries link, users are led to the heart of the site, a list of the tissue libraries for which CGAP genetic data are available. Choosing a link in this list will lead to the genetic library page for that tissue. Each library page includes information about the tissue donor, a link to download all of the expressed sequence tags observed in that library, and brief descriptions of the genes found in the library that seem particularly interesting (either because they code for a large portion of the proteins found in the cell or because they are unique to that library or tissue).

Each gene of interest on the library page is a link to another page of additional data about that gene and the protein for which it codes. The gene pages contain links to maps that show the location of the gene on the human chromosomes, information on other libraries in which the gene is expressed, and links to the DNA sequence that composes that gene.

In many cases, the information on the CGAP site is incomplete—evidence of the enormous amount of work that has yet to be done. But using the Internet to coordinate the effort increases the likelihood that the CGAP will obtain its goal of achieving a comprehensive molecular characterization of the broad spectrum of normal, precancerous, and malignant cells.

